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# DETECTION OF ACOUSTIC SIGNALS OF DIFFERENT DURATION UNDER THE ACTION OF CERTAIN DRUGS

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Translation of "Osobennosti obnaruzheniya zvukovykh signalov razlichnoy dlitel'nosti pri vozdeystvii nekotorykh farmakologicheskimi veshchestvami," Zhurnal Vysshey Nervnoy Deyatel'nosti imeni I. P. Pavlova, Vol. 17, No. 1, 1967, pp. 107-115



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16. Abstract

An experimental verification was made of the hypothesis that there are two spatially distinct mechanisms of the analysis of short and long acoustic signals and that the former is associated with the activity of the temporal levels of the cortex of the cerebral hemispheres. Two drugs with different mechanisms of action were administered to eight healthy adults and, over different periods of time, to intact and operative dogs. Measurements were made of the detection thresholds for ringing of a 1000 Hz tone and white noise with duration of 2, 4, 12, 16, 36, 80, 100, 210, 300, 400, 500, and 1000 msec. It was found that caffeine causes decreases in the detection threshold for short signals ($t \leq 10$ msec), while amphetamine causes these changes for longer signals ($t \geq 10$ msec).

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# DETECTION OF ACOUSTIC SIGNALS OF DIFFERENT DURATION UNDER THE ACTION OF CERTAIN DRUGS /107*

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When the role of the cortical levels of the auditory system in the detection and discrimination of acoustic signals of different duration was investigated (Baru et al. [2-4] and Khanashvili [23]), it was shown that the thresholds of detection and discrimination with respect to frequency and intensity of short sounds ($t < 16$-$20$ msec) are significantly increased upon damage or removal of the cortex of the temporal lobe. In addition, in these studies, as well as in earlier work (Belenkov [5], Mering [16], Kalinina [13], Neff [29], Goldberg and Neff [25], Rosenzweig [31], Raab and Ades [30], and others), it was found that in animals following the removal of the auditory cortex and retrograde degeneration of the medial geniculate bodies, but with preservation of the inferior corpora quadrimena exact discrimination with respect to frequency and intensity of acoustic signals longer than 1 sec was retained. After removal of the auditory cortex and the inferior corpora the discrimination of the intensity persisted, but the differential threshold rose by 5-7 db. Discrimination of frequency was partially disturbed after total transection of the colliculi of the inferior corpora quadrimena.

Based on these data as well as the results of determining the critical total for the summation of primary responses to acoustic signals of different duration recorded from the cortex of the temporal lobe (Gershuni et al. [10,11]), it was hypothesized that there are two spatially distinct mechanisms of the analysis of short and long acoustic signals and that the former is associated with the activity of the temporal levels of the cortex of the cerebral hemispheres (Gershuni [9]).

* Numbers in the right margin indicate pagination in the foreign text.

In this present study we attempted to verify this hypothesis, by studying the changes in the detection thresholds for signals of various duration in conditions of stimulation principally of the cortical or subcortical and cortical levels of the nervous system. For this purpose, we used drugs with different action mechanisms -- caffeine and amphetamine. Caffeine was used as an agent directly acting on the cortex of the cerebral hemispheres, while amphetamine acts primarily on the adrenergic structures of the reticular formation. The stimulating action of caffeine and phenamine on the conditioned-reflex activity was shown by a number of authors; the effect of amphetamine on the defensive conditioned reflexes is especially substantial (see reviews by Fedorov [22], Pavlov [18], Mikhel'son and Shchelkunov [17], Weiss and Laites [34], Carpenter [24], and others.

The effect of these agents on the sensitivity of analyzers has been little investigated. Studies by M. I. Vinogradov et al. [8] showed that when the absolute thresholds for tonal signals are increased through amphetamine fatiguing (in doses of 12-18 mg) caused a reduction in the audibility of the ringing of 100, 2000, and 8000 Hz tones of duration 2-5 sec. It was /108
also shown (Aleksanyan and Mikhaleva [1]) that the visual thresholds after administration of amphetamine either were reduced or were equal to the maximum sensitivity detected in control experiments. Yu. A. Klaas [14] observed after the administration of specific doses of caffeine and amphetamine that there was a reduction in the binaural threshold; here the monaural thresholds for the detection of signals with duration of 1-2 sec remained essentially unchanged [1] after these agents had been administered.

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[1] It should be noted that Yu. A. Klaas used caffeine in the same doses as in our experiments, but lower doses of amphetamine (0.01). Only to one subject was amphetamine administered in a dose of 0.02 g. Yu. A. Klaas observed prolonged and persistent decrease in the monaural threshold for this subject (Fig. 5 and Table 2 in his paper).

## Methods

In this study, changes in the detection threshold for acoustic signals with different duration were investigated in eight healthy adult subjects after the administration of caffeine and amphetamine. Measurements were made of the detection thresholds for ringing of a 1000 Hz tone and white noise with the duration values as follows: 2, 4, 12, 16, 36, 80, 100, 210, 300, 400, 500, and 1000 msec. In addition, in experiments on animals (four dogs) a study was made of the effect of these agents on the detection thresholds for acoustic signals of the same duration before and after removal of the auditory cortex.

The subjects were selected in the 20-30 year age range with normal hearing; their hearing was tested by the usual method of tonal audiometry.

A block diagram of the experimental setup is in Fig. 1.

An electronic switch built in the laboratory (Lebedev /15/) provided for switching on segments of a sine curve in the zero phase, since with this switching the transient distortions were least pronounced. The acoustic generator was a TD-6 electrodynamic telephone. The amplitude characteristic of the acoustic system in the working range of intensities was linear. The time constant of the telephone connection was 0.6 msec.

The experiments were conducted in a sound-proofed chamber; the connection between the tester and the subject was via a microphone. The thresholds were measured based on an arbitrary motor response -- lifting the wrist in response to the acoustic signal, monaurally via a telephone secured to the subject's head.

For comparability of the results of the human and animal investigation, the detection thresholds were measured by the cutoff method. A series of signals decreasing in intensity was presented. The signal intensity was measured by steps, beginning with 0.5 neper, and then with increasing proximity to the threshold -- by steps of 0.1 neper. The threshold was taken as the lowest intensity of signal that was detected by a subject with a probability of 0.5.

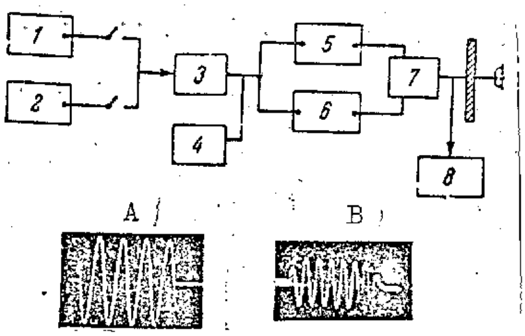


Fig. 1. Block diagram of setup:
1. ZG-12 acoustic generator
2. white noise generator
3. electronic switch
4. VZ-2A lamp voltmeter
5 and 6. attenuation boxes, calibrated in nepers
7. commutator
8. S1-4 oscillograph
A. electrical shape of signal
B. acoustic shape of signal

In the animal experiments use was made of the V. P. Petropavlovskiy motor defensive method [19]. It has the advantage that the raising of a paw by the animal switches on the electric current and therefore, with a strong conditioned reflex responses can be obtained to 200-300 signals in a single experiment. The paw was stimulated with electric current in this experiment no more than 10-15 times. In addition, the relatively immobile position of the animal's head during the experimental period, the absence of gaits and movements of the head associated with the act of eating inevitable in other conditioned-reflex techniques permitted reliably securing electrodes to the animal's head and conducting monaural measurement of thresholds.

The investigation began with the preparation and training of the animal: a conditioned reflex was produced in the form of the raising of a paw at acoustic signals; the animals were trained to respond to signals of various duration and intensity (from 1 to 1000 msec and from 80 db above the threshold to the threshold values). Then the detection thresholds were measured for the ringing of white noise and 1000 Hz tones of various duration. A detailed description of the method was given in our earlier report (Baru [3]).

Following the investigation with the intact dogs of the ef- /109
fect of the drugs on the detection thresholds for acoustic signals of various duration, the auditory cortex was removed in both hemispheres. The operation was performed under inhalational intratracheal anesthesia with an oxygen-ether mixture, which was administered through an intubation tube. The medullary substances was removed subpially with an aspirator.

The removal was carried out in two procedures with an interval of 7 months, during which the effect of the drugs on the detection threshold for acoustic signals was investigated. The superior levels of the anterior and posterior sylvian gyri of two dogs (No. 1 and No. 2) were removed, along with the superior sections of the anterior and posterior ectosylvian and suprasylvian gyri, and all of the medial ectosylvian and suprasylvian gyri. In the case of the third dog (No. 4), the medial and the anterior ectosylvian and suprasylvian gyri and the superior level of the anterior sylvian gyrus were removed. From above, the region of damage extended to the ectolateral, and from beneath -- to the anterior rhinal gyrus. After the first and second operations, the threshold measurements were begun in 8-12 days. Before the completion of the investigation, the animals were sacrificed and the area of removal (see Baru [3]) was inspected in serial preparations of the brain, Nissl-stained.

In preliminary experiments, the subjects were conditioned to threshold measurements and effective doses and duration of drug action were established. Training of the adults took 10-15 experiments, and 40-50 for the animals. Training of the adults and the experimental animals was regarded as completed when the thresholds for the detection of signals with different duration were stabilized, and the difference between the threshold intensities for the ringing of white noise with a duration of 1000 and 2 msec was 24.0±2.3 db for the adult subjects, that is, close to the data described in the literature (see review by Zwislocki [33]). For the intact dogs, the difference between the threshold intensities of the ringing of white noise with a duration of 1000 and 2 msec was 29.0±2.6 db, and for the ringing of the 1000 Hz tone -- 30.2±1.5 db.

In the preliminary experiments it was established that caffeine administered per os in the form of the sodium benzoate salt in doses of 0.2-0.4 g caused a maximum decrease in the threshold intensities in 35-45 min after administration. The duration of its action was 20-40 min. Amphetamine administered in the same way reduced the detection threshold at a dose of 0.015-0.02 g. This effect set in in 30-40 min and lasted 3-4 hr after the administration of the agent. In several experiments, the thresholds after administration of amphetamine were reduced also for the next 1-2 days.

To study the effect of the drugs, the following experimental procedure was established. For 30-40 min the detection thresholds for acoustic signals with different duration were measured. Here the experiment always began and ended with the measurement of the detection thresholds for the ringing lasting 1000 msec. The signals of other durations were presented in random order. After measurement of the thresholds, the test agent was administered (caffeine, amphetamine, or a placebo). Then, 35-40 min after the administration of the agent the thresholds were measured again in the same sequence. In each investigation (experiment) the measurement of the thresholds for signals of all the durations indicated was carried out not fewer than three times before, and three times -- after the administration of the corresponding agents. After the administration of amphetamine, in a number of the experiments the thresholds were also measured in 2, 3, and 4 hr.

The number of experiments involving measurement of the detection thresholds for acoustic signals after the administration of the drugs is presented in Table 1.

TABLE 1. NUMBER OF TESTS WITH ADMINISTRATION OF CAFFEINE AND AMPHETAMINE

| Subjects investigated | Number of subjects | Intact animals | | Animals after removal of auditory cortex | | | | Total |
|---|---|---|---|---|---|---|---|---|
| | | Caffeine | Amphetamine | homolateral ear relative to extirp. side | | contralateral ear relative to extirp. side | | |
| | | | | caff. | amphet. | caff. | amphet. | |
| Subjects | 8 | 37 | 25 | | | | | 62 |
| Animals (intact) | 4 | 8 | — | 7 | 6 | 21 | 8 | 46 |

* In the table are included experiments on the determination of effective doses and duration of action of the agents administered.

Statistical treatment of the measurements involved estimation by Student's t criterion of the confidence of the difference of the means in correlated samplings (Plokhinskiy [20] and Urbakh [21]).



## Results of Investigation /110

The results of the investigations on the adult subjects are in Table 2.

From Table 2 it is clear that after caffeine was administered (in 40-80 min) a decrease in the detection thresholds for the ringing of white noise shorter than 16 msec was observed; the decrease was statistically reliable to a high confidence level. After the administration of amphetamine, the detection thresholds in this range of signal durations (shorter than 12 msec) remained unchanged, but were reduced through the rest of the signal duration range.

TABLE 2. DIFFERENCE BETWEEN THRESHOLD INTENSITIES FOR THE RINGING OF WHITE NOISE OF VARIOUS DURATION BEFORE AND AFTER THE ADMINISTRATION OF CAFFEINE AND AMPHETAMINE (MEAN DATA FROM 75-100 PAIRED MEASUREMENTS CONDUCTED ON EIGHT SUBJECTS)

| Signal duration, msec | Caffeine 0.2-0.4 g diff. db d+Sd | P | Amphetamine 0.15-0.02 g diff., db d±Sd | P |
|---|---|---|---|---|
| 1000 | 0,44±0,25 * | Unreliable | 6,10±0,79 | 0,001 |
| 500 | 0,4 * | » | 6,50±1,00 | 0,001 |
| 400 | 0,3 * | » | 6,60±0,72 | 0,001 |
| 300 | 0,4 * | » | 5,29±0,82 | 0,001 |
| 260 | 0,3 * | » | 5,25±0,84 | 0,001 |
| 210 | 0,4 * | » | 4,90±0,94 | 0,001 |
| 100 | 0,20±0,29 * | » | 3,90±0,87 | 0,001 |
| 80 | 0,71±0,30 * | 0,05 | 3,30±0,88 | 0,001 |
| 36 | 1,48±0,50 | 0,01 | 3,02±0,97 | 0,01 |
| 16 | 1,78±0,45 | 0,001 | 2,16±1,02 | 0,02 |
| 12 | 2,60±0,42 | 0,001 | 1, 3±0,33 | 0,002 |
| 4 | 3,70±0,39 | 0,001 | 0,32±0,39 * | Unreliable |
| 2 | 5,40±0,57 | 0,001 | 0,07±0,67 * | » |

Remark. d is the difference between the threshold values. Sd is the mean error of the difference.

* The difference between the detection thresholds is smaller than the error of measurement, since in establishing the threshold values the signal intensities were measured in steps of 0.1 neper (0.87 db).

Some data obtained in several experiments disclosed some differences. In all cases, when caffeine was administered more thresholds were reduced for short signals, while in some experiments the changes ended for duration values of 12-16 msec, and there were no changes for signals with longer duration. In a small number of experiments (four out of 37) the thresholds were reduced for even longer signals (to 60-100 msec), but the threshold changes were less pronounced than for the short signals. The monaural thresholds for signals with duration of 100-1000 msec remained unchanged in some identical direction after the administration of caffeine[2]. Fig. 2 (A and B) present the

[2] The nature of the effect of caffeine on the monaural detection thresholds for long acoustic signals agreed with the results of the study by Yu. A. Klaas /14/.

extreme results of measuring the thresholds in individual experiments before and after the administration of caffeine.

After the administration of amphetamine in measurements conducted in 40-100 min after the administration of the agent, the detection thresholds for signals shorter than 4 msec, as a rule, were not reduced (Fig. 2 C), and only in one experiment out of 25 was a reduction in the thresholds for 4 msec signals observed.

For measurements conducted 2-3 hr after the administration of the amphetamine, out of 14 measurements a 2-3 db reduction in the thresholds for 2 and 4 msec signals was observed in five measurements. Over the rest of the signal duration range, after amphetamine administration the thresholds were reduced by 4-12 db (Fig. 2 D).

Fig. 3 presents the results of measuring the detection thresholds for the ringing of white noise before and 40 min after the administration of caffeine and amphetamine (mean data from 75-100 paired measurements of all the subjects).

Animal investigations. The results of measuring the threshold intensities of acoustic signals of various duration for four intact dogs before and 40 min after the administration of caffeine (sodium benzoate salt of caffeine, 0.4 g per total weight of animal, pure caffeine 9-11 mg/kg bodyweight) are presented in Table 3.

Clearly, in the dogs a statistically reliable reduction in the thresholds after the administration of caffeine was found, as in the case of the adults, for signals 10, 4, and 2 msec long.

As is known, in small doses caffeine causes a stimulus effect, and in large doses inhibits the conditioned-reflex activity of animals. Accordingly, it is of interest to present the results of two experiments, not included in the Table, on dog No. 3, for which after special treatment (operative preparation, /112

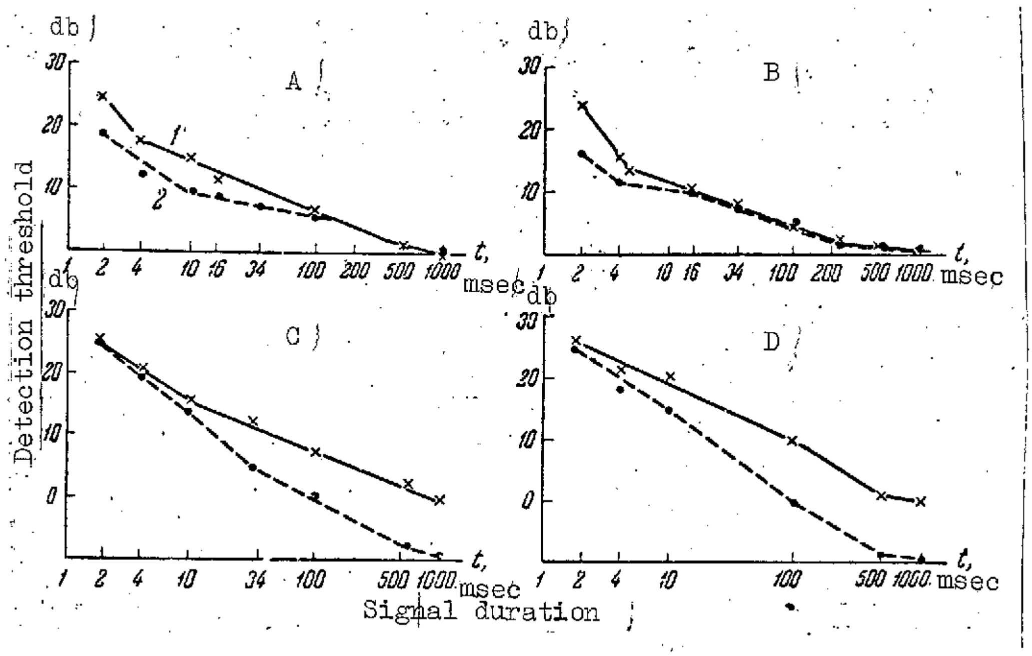


Fig. 2. Dependence of detection thresholds of subjects for ringing of white noise on signal duration.

1. before administration of caffeine and amphetamine
2. after administration

A. investigation of subject X on 16 July 1963, 40 min after administration of sodium benzoate salt of caffeine, 0.4 g

B. investigation of subject X on 5 Aug 1973 40 min after administration of sodium benzoate salt of caffeine, 0.4 g

C. investigation of subject X on 30 July 1963 2 hr after administration of 0.02 g amphetamine

D. investigation of subject S on 6 Aug 1973 2 hr after administration of 0.02 g amphetamine. The threshold for ringing the 1000 Hz tone, measured before the administration of the drugs, was taken as the zero level of reference in decibels.

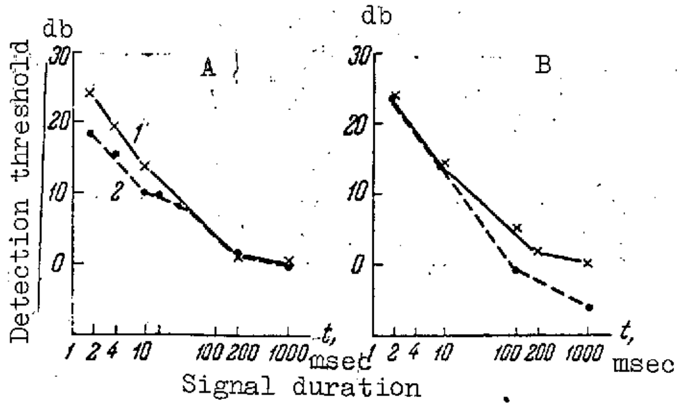


Fig. 3. Effect of administering caffeine (A) and amphetamine (B) on detection thresholds for white noise of various duration (mean data for all subjects):

1. results of measurements before administration of agent
2. after administration

administration of morphine, and anesthesia) an inhibitory effect after the administration of the previously stimulating caffeine dose (sodium benzoate salt of caffeine, 0.4 g) was observed. The monaural threshold for the ringing of the 1000 Hz tone with duration of 1000 msec 40 min after the administration of the agent was 4 db higher; for 120 msec ringings the threshold remained unchanged, and for durations of 1-4 msec it was increased by 12 db, that is, not only a stimulating, but also an inhibitory effect was more pronounced for the short signals.

TABLE 3. DIFFERENCE BETWEEN DETECTION THRESHOLDS FOR RINGING OF WHITE NOISE BEFORE AND AFTER ADMINISTRATION OF CAFFEINE (MEAN DATA FROM 20-25 PAIRED MEASUREMENTS ON FOUR DOGS)

| Signal duration msec | Difference, db $d \pm S_d$ | Confidence $P$ |
|---|---|---|
| 100 | 0.2* | — |
| 500 | 0.4* | — |
| 100 | 0.3* | — |
| 16 | 0.9±0.6 | Unreliable |
| | | 0.01 |
| 10 | 1.2±0.5 | 0.002 |
| 4 | 4.4±0.3 | 0.001 |
| 2 | 4.8±0.6 | 0.001 |

* The difference in the detection thresholds is smaller than the measurement error.

After removal of the cortical projection fibers of the auditory analyzer, as already reported earlier (Baru [3]), when the sound was brought to the ear contralateral to the side of cortical removal, an increase in the detection threshold of the acoustic signals shorter than 16 msec was observed, and when the sound was brought to the ear homolateral to the cortical removal, the thresholds remained unchanged compared with their values in the preoperative period.

For the animals operated on in this manner, after the administration of caffeine, the detection thresholds for signals shorter than 18 msec were reduced for measurements at the ear homolateral to the side of cortical removal, that is, the same correlation as for the intact animals was observed (Fig. 4 A).

TABLE 4. DIFFERENCE BETWEEN DETECTION THRESHOLDS FOR RINGING OF THE 1000 Hz TONE IN DOGS BEFORE AND AFTER ADMINISTRATION OF AMPHETAMINE (MEAN DATA FROM 15-25 PAIRED MEASUREMENTS ON THREE DOGS)

| Duration, msec | Homolateral ear relative to extirp. side | | Contralateral ear relative to extirp. side | |
|---|---|---|---|---|
| | Diff., db $d \pm S_d$ | Confidence $P$ | Diff., db $d \pm S_d$ | Confidence $P$ |
| 1200 | 4.0±0.77 | 0.001 | 3.9±1.1 | 0.001 |
| 201—300 | — | — | 5.2±0.4 | 0.001 |
| 101—200 | — | — | 5.2±0.3 | 0.001 |
| 80 | 3.0±0.3 | 0.001 | 4.9±0.4 | 0.001 |
| 1—7 | 0.6±0.3 | Unreliable | 4.3±1.2 | 0.05 |

When measurements were taken for the ear contralateral to the side of cortical removal 1-3 months after removal of the cortex, caffeine did not cause a statistically reliable change in the detection thresholds for the signals of all the duration values investigated (2, 4, 10, 16, 120, 500, and 1000 msec). Then the auditory cortex of the second hemisphere was removed. Five months after this procedure, in five experiments on three dogs (Nos. 1, 2, and 4) the administration of caffeine caused a 3-4 db drop in thresholds for signals lasting 16, 10, 4, and 2 msec when they were directed either to the right or left ear, since -- naturally -- both ears were contralateral to the extirpation side (Fig. 4 B).

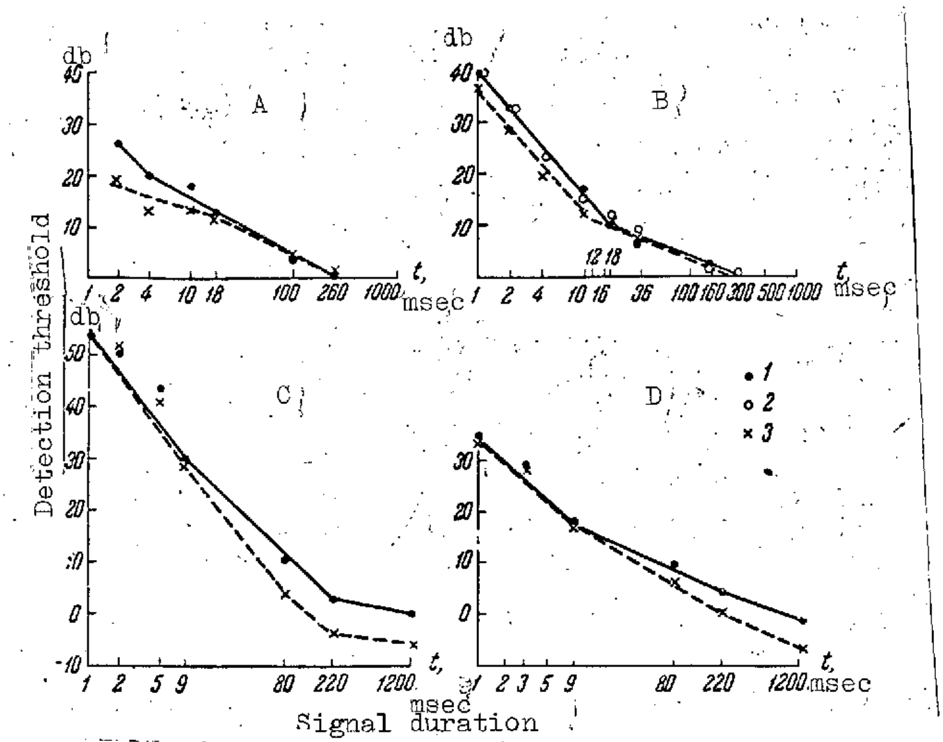


Fig. 4. Effect of administration of sodium benzoate salt of caffeine (0.4 g) and amphetamine (0.02 g) on the detection of ringing of white noise with various duration by dogs after removal of auditory cortex.

A. investigation of dog No. 1 (experiment on 13 Sep 1964) when sound was directed to ear homolateral to side of removed cortex, 35 min after administration of caffeine

B. investigation of dog No. 1 after bilateral removal of auditory cortex. Mean data from five experiments before and after administration of caffeine.

1. before administration
2. after administration of caffeine in the period 10th to 45th day following operation
3. after administration of caffeine 5 months after this operation

C. investigation of dog No. 4 when sound was directed to ear contralateral to removed cortex, before and 40 min after administration of 0.02 g amphetamine (experiment

/caption continued on following page/

/Caption to Fig. 4, concluded/

on 15 Oct 1964)

D. as above, when sound was directed to ear homolateral to side of removed cortex

However, in spite of the reduction in the thresholds after the administration of caffeine, the difference between the thresholds when sound was directed to the ears contralateral to the operative side, before and after removal of the cortex of the temporal lobe, continued to remain statistically reliable. /113

The effect of 0.02 g amphetamine (1.2-1.4 mg/kg animal body-weight) on the detection threshold of acoustic signals with various duration was studied on dogs also after monolateral and bilateral removal of the cortex of the temporal lobe (Table 4).

After amphetamine administration, on the side homolateral to the removed cortex, in four out of six experiments a reduction in the detection thresholds was observed only for signals longer than 10 msec, and in two experiments thresholds for signals of all duration values studied were reduced. When measurements were taken on the side contralateral to the removed cortex, in two out of eight experiments the detection thresholds for ringing of white noise and the 1000 Hz tone were reduced for all the signal duration values investigated; here the reduction was more pronounced for ringing lasting 100-1200 msec. In the remaining six experiments, the thresholds for signals lasting 1-4 msec remained unchanged, while they were reduced for the rest of the signal duration range. The results of measurement of the thresholds after the administration of amphetamine for dog No. 4 when the sound was directed to the ear homo- and contralateral to the side of the removed cortex are shown in Fig. 4 C and D.

Therefore, even in experiments on animals after the administration of amphetamine, the same changes as in the adult subjects /114 were observed -- a reduction in the monaural thresholds for long signals, and only in a number of cases was there a reduction of the thresholds also for short signals.

Thus, in this study it was found that administering certain drugs from the category of nervous system stimulants causes changes in the temporal summation; here caffeine causes these changes in the region of short signal duration values ($t \leqslant 10$ msec), while amphetamine causes these changes in the region of longer signals ($t \geqslant 10$ msec).

V. V. Zakusov [12] has indicated the facilitating effect of certain analeptics (in particular, caffeine, Corazole, and Cordiamine) on the summation of subthreshold impulses necessary to evoke a motor response.

A comparison of the data obtained in the present study and available information on the mechanism of caffeine action (see review of Val'dman [7], Borodkin and Motovilov [6], Jouvet et al. [26], Krupp et al. [27], Monnier and Krupp [28], and Schallek and Kuehn [32]) with the results of an earlier investigation in which an increase in the detection thresholds for short acoustic ringings was noted in patients with localization of damage foci within the cortex of the left temporal lobe and in animals after the removal of the cortical projection levels of the auditory analyzer, this comparison yields further grounds to assume that the detection and discrimination of short sounds ($t < 16$ msec) is associated with the cortical levels of the auditory analyzer.

The absence of a stimulating effect of caffeine after the removal of the auditory cortex when measurements were made on the side contralateral to removal also supports the above hypothesis. The tendency noted toward the recovery of the stimulating action of caffeine on the detection thresholds for short acoustic signals 5-6 months after the operation evidently is associated with the recovery of the activity of the remaining sections of the auditory cortex, since the results of a histological examination of brain preparations from operative animals (No. 1 and No. 2) showed that the cortex of the lower levels of the anterior and posterior ectosylvian and suprasylvian gyri and the cortex deep into the sylvian and ectosylvian sulci was partially preserved.

A reduction in the detection thresholds for acoustic signals lasting 16-1000 msec after the administration of amphetamine evidently is associated with its strong stimulating action on the subcortical levels of the auditory system and to a lesser extent -- on the cortex of the cerebral hemispheres.

Thus, the possibility of a separate effect on the detection thresholds for long and short acoustic signals, found in this study, when psychotropic agents with different action mechanisms are administered agrees completely with the findings of an earlier study in which the disruption of only short acoustic signals after damage or removal of the temporal levels of the cortex of the cerebral hemispheres was found, and provides additional proof that the systems for the analysis of short and long acoustic signals are spatially distinct.

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